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# The Constitution of Barbaloin

## Part I.

BY

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# XC.—*The Constitution of Barbaloin. Part I.*

By Hooper Albert Dickinson Jowett and Charles Etty Potter.

Barbaloin, a crystalline substance obtained from Barbadoes aloes, was first isolated by Smith in 1850 and examined by Stenhouse (*Phil. Mag.*, 1850, [iii], **37**, 481), who assigned to it the formula $C_{17}H_{18}O_7$. With bromine water, it yielded a crystalline tribromo-derivative.

It was further examined by Tilden (Trans., 1872, **25**, 204; 1875, **28**, 1270), who adopted the formula $C_{16}H_{18}O_7$, which was confirmed by Schmidt (*Ber.*, 1875, **8**, 1275). Tilden obtained a crystalline trichloro-derivative, $C_{16}H_{15}O_7Cl_3$, an amorphous acetyl derivative ($C = 58{\cdot}6$; $H = 5{\cdot}4$ per cent.), and found that, by distillation with zinc dust, barbaloin yielded methylanthracene. When oxidised with nitric acid, oxalic, picric, and chrysammic (tetranitro-? 1 : 6-dihydroxyanthraquinone) acids were formed, whilst with chromic acid aloexanthin, $C_{15}H_{10}O_6$ (? tetrahydroxymethylanthraquinone) (Trans., 1877, **32**, 267), was produced. The latter when distilled with zinc dust yielded methylanthracene. Although Tilden did not propose any

constitutional formula for barbaloin, it would appear that he regarded it as an anthraquinone derivative.

Groenewald (*Arch. Pharm.*, 1890, **228**, 115) next examined barbaloin and proposed the slightly different formula $C_{16}H_{16}O_7$. He obtained two crystalline acetyl compounds, which were regarded as tri- and hexa-acetylbarbaloins respectively; his analytical data, however, are not sufficient to decide between these two derivatives, as the difference in the composition of the various acetyl derivatives is within the limits of experimental error. Groenewald also obtained a well-defined crystalline tribromobarbaloin, from which he did not succeed in preparing a crystalline acetyl derivative, but the amorphous compounds obtained gave results lying between those calculated for a tri- and a tetra-acetyl derivative. He found that barbaloin contained no methoxyl groups. Léger (*Compt. rend.*, 1897, **125**, 185) confirmed the formula $C_{16}H_{16}O_7$, and prepared two amorphous derivatives which he regarded as dibenzoyl- and diacetyl-barbaloins. From the mother liquors resulting from the recrystallisation of barbaloin, he isolated a substance differing slightly in its properties from the latter, which he named *iso*barbaloin.

Tschirch and Pedersen (*Arch. Pharm.*, 1898, **236**, 200) have stated that a trihydroxymethylanthraquinone (aloe-emodin) was produced by the aërial oxidation of barbaloin.

Léger (*Compt. rend.*, 1898, **127**, 234) prepared a crystalline triacetyltrichlorobarbaloin and an amorphous tribenzoyl derivative. He stated that Groenewald's tribromobarbaloin was in reality tribromo*iso*barbaloin, and showed that the behaviour of *iso*barbaloin towards acylating agents was similar to that of barbaloin.

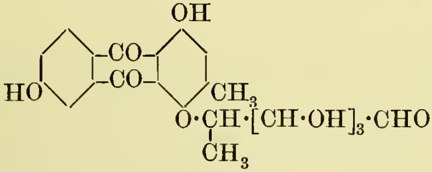
He next (*Compt. rend.*, 1900, **131**, 55) prepared tribromobarbaloin and stated that it differed from the tribromo*iso*barbaloin (Groenewald's tribromobarbaloin) in appearance, solubility, and water of crystallisation. No melting points of the isomerides are given, and the difference in water of crystallisation lies almost within the limits of experimental error, Groenewald having found $4H_2O$, whilst Léger found $3H_2O$, and the latter does not give the experimental details.

Oesterle (*Arch. Pharm.*, 1899, **237**, 81) showed that pure barbaloin, when treated with an alcoholic solution of hydrogen chloride for 24 hours, yielded a trihydroxymethylanthraquinone identical with Tschirch's aloe-emodin and isomeric with the emodin from rhubarb and frangula bark. The aloe-emodin yielded an acetyl compound which Oesterle considered was the diacetyl derivative, but the possibility that it was the triacetyl compound was not excluded. The yield of the emodin from barbaloin was not stated, but no formation of a sugar was observed. He questioned Tilden's conclusions as to the constitution of aloexanthin, but in a later paper (*Arch. Pharm.*, 1903, **241**,

604) he has shown that by the action of chromic acid on aloe-emodin a substance was formed identical with Hesse's rhein, a tetrahydroxymethylanthraquinone isolated from rhubarb. He further showed that aloexanthin was really an impure rhein, and that Tilden's views as to its constitution were correct.

Seel (*Ber.*, 1900, **33**, 3212) gave the results of the oxidation of barbaloin with various reagents, but he was unable to isolate any definite product. With Caro's acid, he obtained tetrahydroxymethylanthraquinone.

Léger (*Compt. rend.*, 1902, **134**, 1111, 1584) stated that by the action of sodium peroxide on barbaloin, formic acid and an aldopentose were formed, in addition to aloe-emodin. He therefore proposed to alter the empirical formula of barbaloin from $C_{16}H_{16}O_7$ to $C_{21}H_{20}O_9$, and suggested the following constitutional formula:—



Barbaloin was thus regarded by Léger as a new type of glucoside which is not hydrolysed by dilute acids.

The evidence adduced in support of this radical change in the formula of barbaloin is by no means conclusive. No analytical proof is given in support of this change, and the analytical data given in Léger's first paper (*loc. cit.*) agree much better with the old than with the new formula. The most important evidence, namely, the molecular weight of the substance or a closely related derivative, is lacking, but the molecular weight of a crystalline substance formerly described as triacetyltrichlorobarbaloin and now regarded as penta-acetyltetrachlorobarbaloin, is given. Unfortunately, the details of the experiment are not recorded. No detailed evidence is furnished of the identification of the sugar formed, and it is merely stated that a lævorotatory syrup was obtained giving all the reactions of an aldopentose.

In a later paper (*J. Pharm. Chim.*, 1904, [vi], **20**, 145), Léger attempted to obtain further proof of the presence of the sugar, which he has named *aloinose*, and indicated that he obtained a crystalline osazone which, however, does not appear to have been actually isolated or examined.

Aschan (*Arch. Pharm.*, 1903, **241**, 341) made a number of analyses of carefully purified barbaloin, free from *iso*barbaloin, and also some molecular weight determination of barbaloin by the boiling point method, using acetone as the solvent; his results confirm the old formula, either $C_{16}H_{16}O_7$ or $C_{16}H_{18}O_7$.

In view of the conflicting statements made regarding barbaloin, and especially in view of Léger's results, we commenced an inquiry into this subject. As our cooperation in this work has been interrupted, it has seemed desirable to publish the results thus far obtained, and the work will be continued by one of us.

The results of numerous analyses and of two molecular weight determinations of carefully purified barbaloin have confirmed the formula, $C_{16}H_{18}O_7$, first proposed by Tilden, although the analytical results are not very different from those required for Groenewald's formula. As our results agree best on the whole for the formula $C_{16}H_{18}O_7$, we shall for the present adopt it. This formula is also supported by the analysis and molecular weight determination of tribromobarbaloin. Léger's conclusions, with regard to the formula $C_{21}H_{20}O_9$ recently proposed by him and as to the constitution of barbaloin, must therefore be abandoned.

We have carefully repeated Léger's experiments on the formation of aloe-emodin by the action of sodium peroxide on barbaloin, but although the conditions were varied, no aloe-emodin could be isolated. On the other hand, Oesterle's experiments on the action of hydrogen chloride in alcohol on barbaloin and the formation of aloe-emodin were confirmed, but the yield of the latter was very small and this line of inquiry was abandoned.

Our next experiments were made with tribromobarbaloin from which a well-defined, crystalline tetra-acetyl derivative was obtained. Tribromobarbaloin, and probably barbaloin, therefore contains four hydroxyl groups. Both these substances yield methylanthracene by distillation with zinc dust.

Whilst we are unable at this stage of the inquiry to offer any suggestions as to the constitutional formula of barbaloin, we wish to point out that the generally accepted view that it contains an emodin (trihydroxymethylanthraquinone) complex is open to serious objection. If it contains this complex, the formula may be written

$$\{[C_{14}H_4O_2(CH_3)(OH)_3]CH_7O(OH)\},$$

and it is difficult to see how so many hydrogen atoms as are contained in the complex $CH_7O$ can be introduced into any possible formula. On the other hand, the formation of small amounts of emodin and other anthracene derivatives renders it probable that it bears some relation to this parent substance. It is possible that it is not a derivative of methylanthracene, but of a reduced anthracene, thus accounting for the large amount of hydrogen contained in the substance.

## EXPERIMENTAL.

Barbaloin was first recrystallised several times from alcohol, but as the melting point (145—150°) of the dried substance was not very sharp, the purified material was again recrystallised from various solvents and the resulting products analysed. The solvents employed were (1) alcohol, (2) ethyl acetate, (3) methyl alcohol, (4) water, and (5) chloroform.

The substance was in each case dried at 105—110° until of constant weight.

(1) 0·0782 gave 0·171 $CO_2$ and 0·0402 $H_2O$. C = 59·6; H = 5·7.
(2) 0·0976 „ 0·213 $CO_2$ „ 0·0476 $H_2O$. C = 59·5; H = 5·4.
(3) 0·133 „ 0·2906 $CO_2$ „ 0·0675 $H_2O$. C = 59·6; H = 5·6.
(4) 0·133 „ 0·290 $CO_2$ „ 0·0668 $H_2O$. C = 59·5; H = 5·6.
(5) 0·1512 „ 0·3312 $CO_2$ „ 0·072 $H_2O$. C = 59·7; H = 5·3.
0·855 in 40 phenol gave $\Delta t$ − 0·51°. M. W. = 310.
0·394 „ „ $\Delta t$ − 0·235°. M. W. = 310.

Of the three formulæ previously proposed

$C_{16}H_{18}O_7$ (Tilden) requires C = 59·6; H = 5·6 per cent. M. W. = 322.
$C_{16}H_{16}O_7$ (Groenewald) „ C = 60·0; H = 5·0 „ M. W. = 320.
$C_{21}H_{20}O_9$ (Léger) „ C = 60·6; H = 4·8 „ M. W. = 416.

These results, in conjunction with those of Aschan (*loc. cit.*), disprove Léger's formula, and, whilst not excluding the formula $C_{16}H_{16}O_7$, point to the correctness of the formula $C_{16}H_{18}O_7$ originally proposed by Tilden. A determination of the specific rotation in 90 per cent. alcohol solution gave the following result:

$$\alpha_D\ -11'; \ l = 0·5 \text{ dcm.}; \ c = 4·4; \ [\alpha]_D\ -8·3°.$$

Léger found in ethyl acetate solution $[\alpha]_D$ − 10·4°.

Attempts to obtain a well-defined crystalline acetyl derivative with acetic anhydride were unsuccessful, and we were unable to confirm Groenewald's results (*loc. cit.*) with regard to the two substances described as triacetyl- and hexa-acetyl-barbaloins. A satisfactory derivative was, however, obtained by acetylating barbaloin with acetyl chloride and crystallising the crude product from light petroleum. As thus obtained, it formed a light yellow, microcrystalline powder, insoluble in water, but soluble in alcohol; it melted at 95—96°, was apparently identical with Groenewald's triacetylbarbaloin (m. p. 92°), and gave, on analysis, results agreeing with those obtained by Tilden and by Groenewald.

0·1471 gave 0·319 $CO_2$ and 0·070 $H_2O$. C = 59·1; H = 5·3.
Tetra-acetylbarbaloin, $C_{24}H_{26}O_{11}$, requires C = 58·8; H = 5·3 per cent.

Although the analytical results do not enable one to differentiate between the different acetyl derivatives, and we were unable to find a satisfactory method for determining the acetyl groups present, yet the results, taken in conjunction with those obtained with tribromobarbaloin, point to the deduction that the substance examined was a tetra-acetyl derivative. Attempts to prepare crystalline chloroacetyl, benzoyl, and methyl derivatives were unsuccessful. The absence of methoxyl groups was confirmed.

When distilled with zinc dust, a small quantity (0·6 per cent.) of a hydrocarbon was obtained which, after recrystallisation from alcohol, melted at 199—200°.

0·0644 gave 0·2212 $CO_2$ and 0·0384 $H_2O$. C = 93·7; H = 6·6.
$C_{15}H_{12}$ requires C = 93·7; H = 6·3 per cent.

The substance was, therefore, methylanthracene.

Sodium peroxide was added to an aqueous solution of barbaloin according to the details given by Léger (*loc. cit.*), and also under varying conditions, but in no case could a substance corresponding to aloe-emodin be isolated. The only evidence of the formation of an anthraquinone derivative was a slight coloration produced by shaking the benzene extract with ammonia.

When barbaloin was treated with hydrogen chloride in alcoholic solution on a water-bath in a reflux apparatus, a very small quantity of a substance having the properties of aloe-emodin was obtained in addition to much unchanged barbaloin. The crystalline substance, after successive crystallisations from glacial acetic acid and toluene, melted at 216—218°, and would thus appear to be identical with the aloe-emodin described by Oesterle (*loc. cit.*). The yield of product was extremely small and all attempts to improve it were unsuccessful.

### *Tribromobarbaloin*, $C_{16}H_{15}O_7Br_3$.

As the experiments with barbaloin did not give very promising results, the tribromo-derivative was prepared and examined. It melted at 191—192° and agreed in all respects with the compound described by Groenewald (*loc. cit.*).

0·0932 gave 0·1165 $CO_2$ and 0·024 $H_2O$. C = 34·1; H = 2·9.
0·1732 ,, 0·1744 AgBr. Br = 42·9.
0·318 in 40 phenol gave $\Delta t$ – 0·11°. M. W. = 535.
$C_{16}H_{15}O_7Br_3$ requires C = 34·3; H = 2·7; Br = 42·9 per cent. M. W. = 559.

*Tetra-acetyltribromobarbaloin*, $C_{16}H_{11}O_7Br_3(C_2H_3O)_4$, was prepared by boiling barbaloin with five to six times its weight of acetyl chloride in a reflux apparatus for half an hour.

The crude product, obtained by distilling off the acetyl chloride and treating the residue with water, was recrystallised from 70 per cent. alcohol; it formed small, yellow needles melting at 135°, and soluble in alcohol but insoluble in water.

0·1332 gave 0·1906 $CO_2$ and 0·0368 $H_2O$. C = 39·0; H = 3·1.
0·211 „ 0·1656 AgBr. Br = 33·4.
0·2044 „ 0·1602 AgBr. Br = 33·3.
$C_{24}H_{23}O_{11}Br_3$ requires C = 39·6; H = 3·1; Br = 33·0 per cent.

The difference in the amount of bromine contained in the several acetyl derivatives which are possible, and the well-defined crystalline character of the compound, enable the composition of this substance to be determined with certainty.

Tribromobarbaloin must therefore contain four hydroxyl groups, and barbaloin in all probability also contains this number.

Attempts to methylate tribromobarbaloin with sodium and methyl iodide were unsuccessful. Treatment with alcoholic hydrogen chloride also gave a negative result, and in both these cases the greater part of the original substance was recovered unchanged. When distilled with zinc dust, methylanthracene (m. p. 199—200°) was obtained.

Numerous experiments have been made with both barbaloin and its tribromo-derivative with various oxidising agents and by fusion with potassium hydroxide, in order to obtain a reasonable amount of definite degradation products, but hitherto without success.

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